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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,325	01/29/2004	Theodora S. Ross	UM-08737	5496

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	
MAIL DATE	**DELIVERY MODE**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,325	ROSS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 8-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 08/30/2007 in response to the previous Non-Final Office Action (5/31/2007) is acknowledged and has been entered.

Claims 1 and 8-15 are pending.

Claims 12-15 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1 and 8-11 are currently under consideration.

New Rejection Necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 1 has been amended to recite a method for determining a risk of prostate cancer, comprising: a) providing a serum sample from a subject suspected of having cancer; and b) detecting the presence or absence of antibodies to Huntingtin Interacting Protein 1 (HIP1) in said serum sample, wherein the presence of antibodies to HIP1 in said sample is indicative of an increased risk of prostate cancer in said subject, and the absence of antibodies to HIP1 in said sample is indicative of a decreased risk of prostate cancer in said subject. In the instant case, the specification teaches the term "risk" in paragraph 0074-0076". For example, the specification (paragraph 0076) teaches that the term "subject at risk for cancer" refers to a subject with one or more risk factors for developing a specific cancer, wherein the risk factors include, but are not limited to, gender, age,

genetic predisposition, environmental exposure, and previous incident of cancer, preexisting non-cancer disease. Thus, while the specification uses the term "risk" in a variety of situation, the limitation of determining the risk of prostate cancer as recited in the instant claims has no clear support in the specification and the claims as originally filed. In particular, the conclusion that the presence of antibodies to HIP1 in said sample is indicative of an increased risk of prostate cancer or the absence of antibodies to HIP1 in said sample is indicative of a decreased risk of prostate cancer in said subject has not clear support in the specification. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

Claims 1 and 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method for determining the risk of prostate cancer, comprising: providing a serum sample from a subject suspected of having cancer; and b) detecting the presence or absence of antibodies to Huntingtin Interacting Protein 1 (HIP1) in said serum

sample, wherein the presence of antibodies to HIP1 in said sample is indicative of an increased risk of prostate cancer in said subject, and the absence of antibodies to HIP1 in said sample is indicative of a decreased risk of prostate cancer in said subject. Thus, the claims encompass determining the probability of a patient having prostate cancer based on the level of HIP1 in a serum a sample.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to determining the risk of prostate cancer, comprising: providing a serum sample from a subject suspected of having cancer; and b) detecting the presence or absence of antibodies to Huntingtin Interacting Protein 1 (HIP1) in said serum sample, wherein the presence of antibodies to HIP1 in said sample is indicative of an increased risk of prostate cancer in said subject, and the absence of antibodies to HIP1 in said sample is indicative of a decreased risk of prostate cancer in said subject. The specification teaches (page 36, lines 1-10) that experiments conducted during the course of development of the present invention have demonstrated that subjects with prostate cancer preferentially exhibit a humoral response to HIP1. For example, the specification provides (page 83, lines 10-14) a humoral response to HIP1 in a TRAMP mouse model for prostate cancer, wherein 10/20 Tag positive TRAMP mice had antibodies in their serum to HIP1 whereas 0/10 normal Tag negative mice had antibodies in their serum to HIP1. In addition to the TRAMP mouse model, the specification teaches (page 82, Example 8) a humoral response to HIP1 in human prostate cancer patients, wherein 5/20 were positive for a humoral response to HIP1 in the prostate cancer patient cohort whereas 9/23 were positive in the "normal" patient cohort. Thus, while the specification appears to imply a nexus between a correlation between cancer detection and autoantibody presence to HIP1 in the TRAMP mouse model, the specification does not appear to clearly indicate whether or not antibodies to HIP1 is indicative of the predicting the risk of the cancerous state in patient suspected of having said cancer. In other words, what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as detecting the presence or absence of cancer. In the instant case, the TRAMP mouse model is an art recognized transgenic model of prostate cancer, which recapitulates many of the features of prostate cancer in humans (*see* Gupta, S. International Journal of Oncology 2004; 25: 1133-1148, of record). For example, Gupta discusses that the TRAMP model has been

used for a wide range of studies including the analysis of growth factors, assessment of intermediate and endpoint markers, markers of angiogenesis, and for evaluating the efficacy of natural agents and synthetic compounds in chemoprevention and therapy of prostate cancer (page 1138, 2nd column, beginning on the bottom to page 1140, 1st column). Thus, while the prior art teaches that the TRAMP mouse model is useful for a variety of studies, the art is silent with regards to the production of a humoral response to a specific cancer related antigen and using these results as a diagnostic marker for cancer. Furthermore, if a molecule such as an antibody to HIP1 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some type of pattern that would allow the claimed antibody to be used in a diagnostic manner. For example, antibodies to HIP1 were found in serum of "normal" patients, as well as patients suffering from prostate cancer as evidenced by the disclosure (page 82, Example 2). Similarly, the specification teaches (page 63, lines 1+) that many proteins such as HIP1 are expressed in normal tissues and diseased tissues. Therefore, one needs to know that antibodies to HIP1 are present only in a cancer patient to the exclusion of normal patients. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing an cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders such as prostate cancer. Moreover, Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful

application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4). Thus, in the absence of any correlation between antibodies to HIP1 with any known disease or disorder, any information obtained from various profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself. Therefore, absent evidence of the antibodies to HIP1 presence including the correlation to a diseased state, one of skill in the art would not be able to predictably use antibodies to HIP1 in any diagnostic setting without undue experimentation.

Reasonable correlation must exist between the scope of the claims and the scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments as they pertain to the instant rejection. In response to the previous enablement rejection, Applicants contend that the specification and the supporting data previously provided by the Applicants (Bradley et al., Cancer Research 65:4126) provide enablement for such embodiments; and further, one skilled in the art (e.g., a clinician trained in screening for prostate cancer such as a primary cancer physician) would know how to interpret such data. For example, Applicants assert that the presence of serum antibodies to HIP1 is indicative of an increased risk of a subject having prostate cancer; and therefore, if a subject is found to have serum antibodies to HIP1, a decision can be made to pursue further diagnostic testing (e.g., a biopsy). Likewise, Applicants assert that the HIP1 marker can be analyzed in combination with other known markers to provide a more thorough risk assessment, upon which a treating physician can use their judgment in selecting appropriate patient care.

These arguments have been carefully considered, but are not found persuasive.

In response to these arguments, the Examiner has reviewed the contents of the 2005 publication, specifically Figures 3 and 4 and agrees with Applicants that it demonstrates that a higher percentage of prostate cancer patients relative to control individuals showed a humoral response to HIP1. However, the Examiner recognizes that the mere presence of autoantibodies to HIP1 does not appear to be indicative of determining the risk of prostate cancer because these normal patients have also been found to generate a humoral response to HIP1. As stated above, if a molecule such as an antibody to HIP1 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some type of pattern that would allow the claimed antibody to be used in a diagnostic manner. For example, the specification teaches that antibodies to HIP1 were found in serum of "normal" patients, as well as patients suffering from prostate cancer (page 82, Example 2). Similarly, the specification teaches (page 63, lines 1+) that many proteins such as HIP1 are expressed in normal tissues and diseased tissues. Thus, contrary to Applicants assertions that the presence of serum antibodies to HIP1 is indicative of an increased risk of cancer, the specification, as well as the 2005 publication, appears to suggest that serum antibodies to HIP1 are expressed in the serum of "normal" patients. Thus, while the Examiner acknowledges Applicants assertions that the presence of serum antibodies to HIP1 could be used in combination with other known markers, any information obtained from various profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself.

Conclusion

Therefore, NO claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

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